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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/402,488	02/16/00	MOLONEY	M 9369-98

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BERESKIN AND PARR
SCOTIA PLAZA
40 KING STREET WEST-SUITE 4000 BOX 401
TORONTO ON M5H 3Y2
CANADA AIR MAIL

EXAMINER	
STEADMAN, D	
ART UNIT	**PAPER NUMBER**
1652	15

DATE MAILED: 05/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/402,488	Applicant(s) MOLONEY ET AL.	
	Examiner David J. Steadman	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *31-40 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30 and 41-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Status of the Application

Claims 1-47 are pending in the application.

Applicants' election without traverse of Group I, claims 1-30 and 41-44 in Paper No. 14, filed 04/12/01 is acknowledged.

Claims 31-40 and 45-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

Drawings

1. The drawings submitted with this application have not been reviewed by a draftsperson at this time. When formal drawings are submitted, the draftsperson will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Specification/Informalities

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent

application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

3. It is suggested that the heading "DETAILED FIGURE LEGENDS" on page 19 of the specification be replaced with "BRIEF DESCRIPTION OF THE DRAWINGS."

4. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. The term "introducing into a host cell an expression vector" in claim 1 (claims 2-19 dependent thereon) is unclear and confusing. The term "introducing into a host cell an expression vector" is not defined by the claim nor the specification and the meaning of this term is unclear. It is suggested that the language be replaced with a term that has a more clearly identifiable meaning, for example, "transforming a host cell with an expression vector".

6. Claim 5 recites the limitation "the polypeptide" in claim 1. There is insufficient antecedent basis for this limitation in the claim. It is suggested that Applicants replace the term "the polypeptide" with "the recombinant polypeptide."

7. Claim 27 is confusing in that the claim recites "a chimeric nucleic acid sequence... ...shown in SEQ ID NO:1 or SEQ ID NO:2." However, SEQ ID NO:2 is the amino acid sequence encoded by SEQ ID NO:1. It is suggested that Applicants replace "SEQ ID NO:2" with their intended SEQ ID NO, for example, "SEQ ID NO:3".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5-22, and 23-30, and 41-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 (claims 5-19 dependent thereon), 2, 3, 20 (claims 24-30 dependent thereon), 21, 22, 41 (claims 43 and 44 dependent thereon), and 42 are directed to a genus of nucleic acids encoding autocatalytically maturing zymogens comprising a pro-peptide from an autocatalytically maturing zymogen fused to a heterologous polypeptide. The specification teaches only seven representative species of such prot-peptides from an autocatalytically maturing zymogens, i.e., the pro-peptides of chymosin, trypsinogen, pepsin, HIV-1 protease, pepsinogen, cathepsin or yeast proteinase A. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a pro-peptide from an autocatalytically maturing zymogen. Given this lack of description of representative species encompassed by the genus of the claim, the specification

fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

9. Claims 1-30 and 41-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the preparation of recombinant hirudin or carp growth hormone (cGH) by transforming a host cell with a nucleic acid encoding a zymogenic fusion protein consisting of the chymosin pro-peptide fused to hirudin or cGH, expressing a fusion protein, and adjusting the pH to between 2 and 4.5 in order to activate the cleavage of the chymosin pro-peptide from the hirudin or cGH or a chimeric nucleic acid sequence therefor and compositions thereof, does not reasonably provide enablement for a method of preparation for a recombinant polypeptide by transforming a host cell with a nucleic acid encoding any pro-peptide derived from an autocatalytically maturing zymogen upstream of a nucleic acid encoding said recombinant polypeptide, expressing any pro-peptide fusion protein and altering the environment in order to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequence therefor and compositions thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-30 and 41-44 are so broad as to encompass a method for the preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding any pro-peptide derived from an autocatalytically maturing zymogen upstream of a nucleic acid encoding said recombinant polypeptide, expressing a pro-peptide fusion protein and altering any *in vitro* or *in vivo* environmental conditions to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequences therefor and compositions thereof. The scope of the claims is

not commensurate with the enablement provided by the disclosure with regard to the extremely large number of autocatalytically maturing zymogens and environmental alterations leading to cleavage of the pro-peptide as broadly encompassed by the claims. Since the amino acid sequence of a zymogen determines its structural and functional properties, predictability of which changes can be tolerated in a zymogen's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the pro-peptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function under a particular environment. However, in this case the disclosure is limited to a method for the preparation of recombinant hirudin or cGH by transforming a host cell with a nucleic acid encoding the pro-peptide of chymosin upstream of a nucleic acid encoding hirudin or cGH, expressing a fusion protein, and adjusting the pH to between 2 and 4.5 in order to activate the cleavage of the chymosin pro-peptide from the hirudin or cGH or a chimeric nucleic acid sequence encoding a fusion protein comprising a nucleic acid encoding the chymosin pro-peptide upstream of a nucleic acid encoding hirudin or cGH and compositions thereof.

The specification does not support the broad scope of the claims which encompass a method for the preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding any pro-peptide derived from an autocatalytically maturing zymogen upstream of a nucleic acid encoding said recombinant polypeptide, expressing a pro-peptide fusion protein and altering any *in vitro* or *in vivo* environmental conditions to cleave the pro-peptide from the recombinant polypeptide or a chimeric nucleic acid sequence encoding a fusion

protein comprising a nucleic acid encoding any pro-peptide derived from an autocatalytically maturing zymogen upstream of a nucleic acid encoding said recombinant polypeptide and compositions thereof, because the specification does not establish: (A) all *in vitro* or *in vivo* environmental, pH, salt, and/or temperature conditions that will result in specific cleavage of any pro-peptide derived from an autocatalytically maturing zymogen from the recombinant polypeptide without affecting recombinant polypeptide activity; (B) the ability to specifically cleave any pro-peptide derived from an autocatalyically maturing zymogen without nonspecific cleavage of the recombinant polypeptide, as some recombinant polypeptides will possess a pro-peptide cleavage site, resulting in nonspecific cleavage of the recombinant polypeptide; (C) the predictability that pro-peptides can be cleaved by zymogens that are heterologous to the pro-peptide and/or can provide further autocatalytic cleavage in the absence of the mature portion of the zymogen from which the pro-peptides are derived; (D) the general tolerance of a fusion protein comprising a pro-peptide derived from an autocatalytically maturing zymogen to modification and extent of such tolerance; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for the preparation of a recombinant polypeptide by transforming a host cell with a nucleic acid encoding any pro-peptide derived from an autocatalytically maturing zymogen upstream of a nucleic acid encoding said recombinant polypeptide, expressing a pro-peptide fusion protein and altering any *in vitro* or *in vivo* environmental conditions to cleave the pro-peptide from the recombinant polypeptide or a

chimeric nucleic acid sequence encoding a fusion protein comprising a nucleic acid encoding any pro-peptide derived from an autocatalytically maturing zymogen upstream of a nucleic acid encoding said recombinant polypeptide and compositions thereof. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 1-7, 9-13, 15, 19-26, 28-30, and 41-44 are rejected under 35 U.S.C. 102(a) as being anticipated by Moloney (WO 96/21029). Claims 1-7, 9-13, 15, 19-26, 28-30, and 41-44 are drawn to a method for the preparation of a recombinant polypeptide by introducing into a host cell an expression vector comprising: a chimeric nucleic acid encoding a fusion protein comprising a nucleic acid encoding a pro-peptide from an autocatalytically maturing zymogen and a nucleic acid encoding a heterologous polypeptide immediately downstream of the nucleic acid encoding the pro-peptide, a chimeric nucleic acid encoding a fusion protein comprising a nucleic acid encoding a pro-peptide from an autocatalytically maturing zymogen and a nucleic

acid encoding a heterologous polypeptide immediately downstream of the nucleic acid encoding the pro-peptide, and compositions thereof. Moloney teaches a method for expression and release of a recombinant polypeptide in a host cell by: a) introducing into a host cell a chimeric DNA sequence comprising: 1) a first DNA sequence capable of regulating transcription in said host, 2) a second DNA sequence encoding a recombinant fusion polypeptide comprising a DNA sequence encoding a recombinant polypeptide and a DNA linker sequence encoding an amino acid sequence that is specifically cleavable by enzymatic or chemical means located between the sequences encoding an oleosin gene and a recombinant polypeptide and 3) a third DNA sequence encoding a termination region functional in the host; b) growing the host to produce the recombinant fusion polypeptide, (p 3, lines 14-26) and also teach that the peptide linker preferably includes a protease target motif (p 20, line 1). Moloney et al. teach that the recombinant polypeptide(s) to be produced as a fusion may include growth hormones (p 24, lines 19 and 20), the anticoagulant hirudin (p 25, lines 4 and 5), additives for animal feeds (p 24, line 17), for use in the food industry (p 24, line 27), proteins with a therapeutic or diagnostic value (p 25, lines 1-2) and teach that the recombinant protein "may be capable of undergoing self-release" and provide an example as follows: "the proteolytic enzyme chymosin undergoes self-activation from a precursor to an active protease by exposure of the precursor to low pH conditions. Expression of the chymosin precursor/oleosin fusion protein to conditions of low pH will activate the chymosin. If a chymosin recognition site is included between the oleosin and the chymosin protein sequences, the activated chymosin can then cleave the fusion proteins. This is an example of self release that can be controlled by manipulation of the conditions required for enzyme activity" (p 29, lines 3-10). Moloney further teaches a specific example of expression of

an oleosin/hirudin gene fusion in *Brassica napus* by disclosing that a hirudin gene fusion was prepared with the C-terminal end of an *Arabidopsis thaliana* oleosin gene and that the gene sequences for oleosin and hirudin were separated by codons for an amino acid sequence encoding a Factor Xa endoprotease cleavage site and that huridin can be cleaved from the oleosin by the use of the Factor Xa cleavage site built into the fusion protein (p 46 and 47) and additionally teaches that the fusion protein can be an oleosin/chymosin fusion (p 52, lines 6-10). Moloney also teaches "for uses where the fusion protein contains a peptide hormone that is released upon ingestion, the protease recognition motifs may be chosen to reflect the specificity of gut proteases to simplify the release of the peptide" (p 20, lines 7-10). This anticipates claims 1-7, 9-13, 15-26, 28-30, and 41-44 as written.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Moloney (WO 96/21029) in view of McCaman et al. (J Biol Chem 261:15345-15348). Claim 8 is drawn to a method for the preparation of a recombinant polypeptide by altering the pH to a range of 2 to 4.5.

Moloney discloses the teachings as described above. Moloney does not explicitly teach altering the pH to a pH from about 2 to about 4.5.

McCaman et al. teach that the zymogen form of chymosin is activated at pH 2.0 to form a pseudochymosin product by removal of residues 1-27 and is further processed to chymosin at a pH of 4.5 by removal of residues 1-43.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Moloney and McCaman in order to cleave the recombinant polypeptide from the pro-peptide using a pH between 2 and 4.5. One would have been motivated to use a pH range between 2 and 4.5 because of the teaching of McCaman who taught chymosin is activated between a pH of 2 and 4.5. One would have a reasonable expectation of success because of the results of Moloney and McCaman. Therefore, claim 8, drawn to a method for the preparation of a recombinant polypeptide by altering the pH to a range of 2 to 4.5 would have been obvious to one of ordinary skill in the art.

Conclusion

12. No claim is in condition for allowance.

Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4242. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1:6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or

proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1602